"CLINCO - PATHOLOGICAL STUDY OF ACUTE RENAL COLIC AND EVALUATION OF DICLOFENAC SODIUM AS AN ANALGESIC"

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C E R T I F I C A T E

This is to certify that the work of Dr. Mukesh Chaturvedi on " CLINICO-PATHOLOGICAL STUDY OF ACUTE RENAL COLIC AND EVALUATION OF DICLOFENAC SODIUM AS AN ANALGESIC ", which is being presented by him for M.S. (General Surgery) examination 1991, has been carried out in the department of Surgery.

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C E R T I F I C A T E

This is certified that the work embodied in this thesis entitled " CLINICO-PATHOLOGICAL STUDY OF ACUTE RENAL COLIC AND EVALUATION OF DICLOFENAC SODIUM AS AN ANALGESIC " has been carried out by Dr. Mukesh Chaturvedi, under my guidance and supervision.

The method of work and results obtained have been checked by me from time to time and are genuine to the best of my knowledge.

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(GUIDE)

A C K N O W L E D G E M E N T

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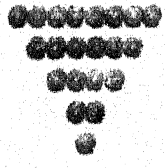

INTRODUCTION

INTRODUCTION

According to Greek Mythology " the first men enjoyed complete happiness in golden age. They lived like a god, Free from worry and fatigue, old age did not afflict them, they rejoiced in continual festivity ". Their lot did not include immortality, but at least they died as though overcome by sweet slumber, But Pandora, opened her box and let loose all the afflictions of mankind.

Disease is as old as life on earth. With ever new ways, men always the experimenter, fought diseases from the day he was born on earth. For thousands of years he was a looser and only the strongest men survived.

Due to ignorance, the disease was considered to be caused by evil spirit and special prayers to various Gods were offered and superstitious reigned brutal and fake remedies were order of the day. Physicians jumped up and down on a sick child's stomach to drive disease out of him. They prescribed frog's eyes to cure human eye troubles. Diseases became "conquerer" and epidemics slaughtered countless millions. Magical symbols, Rx, which is representation of eye of Horus, the Egyption God of healing and staff with two snakes, staff of hermes (Mercury), mythical messenger of God's are being used by physician even today.

Though the malady of stone disease was known to physicians of earlier age than Hippocrates- no definitive cure except operative removal of stone was found to be satisfactory. The operation, itself was very dangerous and often fatal so that, even Hippocrates in his famous oath wanted physicians to refrain themselves from operation and leave it to be done by specialists in this art. " I will guard my life and my art, I will not use the knife on sufferers from stone, but I will give place to such as craftmen therein ".

Several words are used to describe the causative substance of this disease. Stone is the most common term, the word stone is derived from Greek word " Steer ", which means " Hard ".

'Concretions' - is a term derived from latin word "Concretus " concrete : a mass formed by coalescence of seperate particles of matter in the body.

"Lithiasis " - means formation of concretions in the body. It is derived from Greek word 'Lithos' - means "stone" 'lithia' is white crystalline oxide of lithium.

'Calculus' is a latin word, which means pebble or stone in bladder, a concretions of mineral salts around organic material found in hollow organ or ducts. This terms really indicate one of theories of stone

"Colic" - is a term derived from the latin word Colica (Kol-i-Kha), colic means acute paraoxysmal abdominal pain.

Inspite of great progress made since Hippocratic era, the cause of stone formation is not clear. Many theories have been put forward to explain the cause and development of urologic calculi; Nucleation theory, stone matrix theory, inhibitors of crystallization theory but none have been able to answer all the questions. In all probability, stone disease may be due to interaction of multiple factors, many of which are yet unknown.

By 1950, investigators began to report some significant physiologic observations that were associated with production of urinary calculi. These included the importance of diet especially in association with uric acid bladder calculi (Gutman and Yu 1968).[19]

Hypercalciuria was clearly defined as one factor contributing to the formation of calcium calculi and hypercalciurea due to hyperparathyrodism was identified and separated from idiopathic hypercalciurea. Importance of Nucleation of stones in kidney was studied intensively by Randall (1937), who describe his favours " Randall plaque", Urinary crystals and colloids were described, and the crystalloids and colloid composition of all

stones was determined. The effect of infection on stone formation was noted to be different from effects of excessive excretion of crystalloids in the absence of infection. Much ground work was laid for the world-wide resurgence of research into the etiology and prophylaxis of urolithiasis that followed world-war II.

Anderson[2] (1973) presents an interesting multifaceted theory of epidemiology of urinary calculi. He notes that the incidence of upper urinary tract calculi varies greatly with age, anatomic site and geographical distribution and that there are unexplained increases during different periods of history. He feels therefore that there are at least two separate epidemiological factors involved in the genesis of urinary calculi. The first of these may be considered intrinsic. Intrinsic factors are related to the inherited biochemical or anatomic make up of individuals. For example African Bantu natives and the related North American Negros tend to have very few urinary calculi (Modlin[55] 1967, Pantenowitz[60] et al, 1973). A subcategory of this racial or ethnic factor includes any familial tendency towards generation of calculi. Familial inheritence of calcium stone disease has been reported and reviewed by Finlayson[17] (1974) no true sex linked inheritence of urinary lithiasis has been

defined, but Boyce[8] 1973 have reported that male relatives of patients with hypercalciuric stone disease were more often afflicted than female relatives. Intrinsic factors of urolithiasis, then included ethnic, racial or familial background and any inherited physicological or anatomic predisposition of urinary calculi.

Superimposed upon these apparent intrinsic factors are those that Anderson terms extrinsic. Another terms for these might be environmental factors. These include climate, water available for drinking dietary patterns or populations and of household of people with urinary calculi, the presence or absence of trace elements in food stuffs and drinking water, differing age and sex distributions of types of calculi; and different occupations.

Recently Coe F.L. and Park J.H.[11] (1988) observed that renal calculi are concretions consisting of crystals and matrix of organic matter. Crystals usually constitute the matrix predominant portion (90%) of the mass of most calculi but those occuring as a consequence of urinary tract infections have a higher proportion of matrix material. Renal calculi are to be distinguished from calcific deposits within renal parrenchyema. Such deposits occuring at sites of previous inflammation or degenerative changes, are designated by the term "Nephro-calcinosis".

Klahr, S[32] et al (1986) reported that the type of calculous disease is modified by geogrephic factors, sex, race and probably diet. Males are affected more than females and the peak age of onset is between 30-50 years. Familial and hereditory predisposition to stone formation has long been known. Many of the inborn errors of metabolism, such as gout, cystinuria and primary hyperoxaluria, provide good example of hereditary disease, characterized by excessive production and excretion of stone formation substance.

Arruda[1], J.A.L. (1983) reported that there are many causes for the initiation and propagation of stones, the most important determinant is an increased urinary concentration of the stones' constituents, such that it exceeds their solubility in urine (Supersaturation). A low urine volume in some metabolically normal patient may also favour supersaturation. Kill[33] F (1987), It can thus be appreciated that increased concentration of stone consitituents, change in urinary pH, decreased urinary volume and the presence of bacteria influence the formation of calculi. However many calculi occurs in the absence of these factors, and conversely, patient with hypercalciuria, hyperoxaluria and hyperuricosuria often do not forms stones. It has, therefore postulated that change in urinary content

of mucoproteins that, form the organic matrix of urotiths may be important or alternatively, that there is deficiency in inhibitors of crystal formation in urine. The list of such inhibitors is long including pyrophosphate, diphosphonate citrate and recently described glycoprotein called nephrocalcine, but no consistent deficiency of any of these substances has been demonstrated in stone formers (Klahr[32] S et al, 1986).

Arruda[1] J.A.L. (1983) reported that the renal colic arises from the kidney associated with the inflammation or obstruction at the level of the pelviureteric junction. Stones are of importance when they obstruct urinary flow or produce ulcerations and bleeding. They may be present without producing any symptoms or significant renal damage. In general small stones are most hajardous, as they may pass ureter. Producing pain referred to as colic as well as ureteral obstruction. Larger stones can not enter the ureters and are more likely to remain silent within renal pelvis. Commonly, these larger stone first manifest themselves by hematuria. Stone also predispose to superimposed infection, both by their obstructive nature and by the trauma they produce.

The pain of acute renal colic is usually severe and demands immediate and complete

relief. The established mode of therapy are (a) Narcotic analgesic often combined with spasmolytic agent, side effect and the risk of drug addiction indicate the need for an alternatives to narcotics (b) Non narcotics analgesic antispasmodic combinations Baralgan is widely used example of the second group. It is a combination of dipyrone, which is an analgesic, a benzophenone components. Which is a smooth muscle relaxant and a diphanyl derivatives, which has a parasymphatolytic actions.

Marsela[51] F (1980) introduce recently, a third option has become available based on a better understanding of the physiological changes during ureteral obstruction and colic. This ureteric obstruction causes increased synthesis and release of prostaglandins. Lundstam[40] S. (1987) as a result renal pelvis pressure rises, causing renal colic. Prostaglandin inhibitors have been used to relieve the pain of renal colic. (Sahreem L.P. and Carlson[78] (1975).

Edmond[35] C. K. U. (1974) reported that the diclofenac sodium (the sodium salt of 0 - (2, 6 dichlorophenylamino - phenylacetic acid) is a non steroidal antiinflammatory drug a potent prostaglandins synthetase inhibitor. It has been shown to relieve renal colic more effectively than other drugs. Diclofenac is normally advocated for use in painful and inflammatory rheumatic and certain non rheumatic conditions. It is

available in a number of administration forms, which can be given orally, Intramuscular and rectally. Drugs[63] 35 (1988) conveniently, dosage adjustment are not required in the elderly or inthose patients with renal or hepatic impairement. The drug has a relatively short elimination half life, which limits the potential for durg accumulation.

Drugs[63] 35 , 1988 in numerous clinical trials the efficacy of diclofenac is equivalent to that of many newer and established NSAIDs with which it has been compared. As an analgesic i t has a fast onset and long duration of action. When administered intramuscularly, it is at least comparable to and frequently superior to many narcotic and spasmolytic combinations in renal and biliary colic.

Extensive clinical experience has been gained with diclofenac, clearly establishing its safety profile. It is well tolerated compared with other NSAIDs and rarely produce gastrointestinal ulceration or other serious side effects. Thus, diclofenac can be considered as one of the few NSAIDs of 'First choice' in the treatment of acute renal colic.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Anthropologic history provides evidence that urinary calculi existed as long as 7000 years ago or perhaps more. The recognition of different varieties of urinary calculi also resulted in more varieties of medical treatment. During the last decade however, many major advances have greatly improved our understanding of the causes of stone disease. Karpukhin[36] (1961). Although not all calculi can be cured, patients who develop one of the five major types of urinary calculi now have atleast a 50 percent chance of cure or control with medical therapy alone. Surgery continues to be important as one aspect of treatment of urinary calculi, but it is now only one step in total therapeutic or the mentorium for patients with urinary lithiasis.

Urinary lithiasis is one of the most common disease of urinary tract. It occurs more frequently in men than women, a familial predisposition is often encountered. The history of stone disease impiles that many factors might be involved in it's causation; heredity, environment, Age, Sex, Urinary infection, the presence of metabolic disease and dietary excess or deficiencies to review some of these factors, the epidemiological aspects of urinary calculi are helpful.

Epidemiological aspects of urolithiasis

Anderson[2] (1973) presented an interesting multifacted theory of epidemioloy of urinary calculi. He felt that there were at best two seperate epidemiological factors involved in the genesis of urinary calculi.

1. Intrinsic factors
2. Extrinsic factors

INTRINSIC FACTORS

1. Heridity - Numerous authors have noted that urinary calculi are relatively rare in the North American indians, the Negros of Africa and America, and the native born conversely the incidence of stone disease is known to be highest in some of the colder temperature of the world populated primarily by Eurasians and caucasions. Various authors conclude that urolithiasis requires a polygenic defect (more than one genesis involved). In addition, genetic predisposition to urinary lithiasis has partial penetrance, so that the severity of stone disease may differ from generation to generation even though individual has the gene defects necessary for urinary lithiasis.

Rënal tubular acidosis is one heriditory disease that has been certainly associated with frequent episodes of urolithiasis. Cystinuria is a prime example of familial type of urinary lithiasis

that is definitely heriditary.

2. Age and Sex : The peak age incidence of urinary calculi occurs in the third to fifth decades. About 3 males are afflicted for every female. Burkland Rosenberg[65] 1965 have pointed out that the maximum incidence of urinary lithiasis appears to occurs in the 30 to 50 years age group.

Lonsdale[41] (1968) observed the incidence of upper urinary tract calcification approximately equal in male and female at the time of autopsy.

Several authors have commented upon the apparently equal tendency towards urinary lithiasis in males and females during Childhood (Prince and Scardino[62], 1960). This observation completed with reports that increased serum testosterone level resulted in increased endogenous oxalate production by liver led Finlayson[17] (1974) to postulate that lower serum testosterone level may contribute to some of the protection that women (and children) enjoy against oxalate stone disease. Recently, Schramm and Carlson[78] (1975) have demonstrated increased urinary citrate concentration in urine of females, and they postulate that this may aid in protecting female from calcium urolithiasis.

EXTRINSIC FACTORS

1. Geography :- There is noticable increase in urinary calculi in mountainious or tropical areas. Boyce[8] et al

(1959) performed an extensive study of incidence of calculus disease in the united states. Other high incidence areas are the British isles, Scandinavia, Mediterranean countries, Northern India and China (Finlayson[17] 1974).

2. Climatic and seasonal factors : It is difficult to find direct evidence for the influence of climate on occurence of urinary lithiasis. Several authors, however have attempted to show a relationship between higher environmental temperature and increased seasonal incidence of urinary stone disease (Prince and Scardino[62], 1960; Elliott[16], 1975).

Elevated environmental temperature seems to be definitely related to increased risk of stone disease in population capable of forming stones. High temperature increases perspiration which may result in increased concentration of urine. This hyper-concentration could contribute to stone formation in many ways. For example if the individualy has, as noted above, an inborn tendency towards formation of calculi, dehydration would result in decreased urine volume and increased urinary concentration of these molecules as well as excessive urinary acidity. These two changes promote crystalization of the respective molecules. In persons with a tendency to form calcium

calculi, urinary concentration of calcium oxalate and phosphate would increase, large crystal could form, possibly aggregatting into stones. Patient with a tendency towards formation of uric acid or cystine calculi would have an additional risk because acid urine holds much less uric acid and/or cystine in solution. One admonition to stone formers as derived from these studies, then might be to "Keep Cool".

3. Water intake and urinary lithiasis : Two factors involved in the relationship between water intake and urolithiasis are the volume of water ingested as opposed to that lost by perspiration, and the mineral or trace elements content of water supply of the region. One of the prevailing assumption in the literature of urolithiasis is that increased water intake and increased urinary output decreases the incidence of urinary calculi in these patients who are predisposed to the disease. Finalyson[17] (1974) demonstrated that increased urine flow causes a reduction in urine oxalate (concentration). How-ever to be significantly effective a urine output of more than 3600 ml per day would be theoretically necessary.

4. Diet : There can be little doubt that dietary intake of various foods and fluids that result in increased urinary excretion of substances that produce stone has a significant effect on the incidence of urinary calculi. Peculiar dietary excesses may also occur. Such as use of large amount of

worcestershine sauce with its high oxalate content, vegetarian diet, or habitual excessive ingestion of milk products in the form of cream.

5.Occupation : Lonsdale[41] indicated (1968b) that urinary calculi are much more likely to be found in individuals who have sedentary occupations. Blacklock[7] (1969) reported that the incidence of urinary calculi was higher in administrative and sedentary personal of Royal Navy than in manual workers. Anderson[2] (1973) emphasized that the relationship between diet and heredity is the major determinent for urolithiasis, but that occupation is also improtant. Occupation also tends to determine exposure to other factors such as high environemntal temperature that may then increase tendency towards formation of urinary calculi.

Present Theoretical Basis of Etiology of urinary calculi

Modern concepts of urinary calculous disease may be separated conveniently into five major theories.

1. Supersaturation crys talization theory
2. The matrix nucleation theory.
3. The inhibitor absence theory.
4. Epitaxy
5. Combinations of above.

Supersaturation/Crystalization:- Uric acid and cystine calculi form whenever urine with a tendency to remain at

an acid pH becomes over saturated with uric acid or cystine. Magnesium amonium phosphate calculi form whenever the product of concentration of these ions exceed the saturation product and when the urine remains alkaline for long periods of time.

Inhibitor lack : Blacklock[7] (1969) have produced such a theory for calcium oxalate urinary lithiasis. Their study suggest that for calcium oxalate calculi an index of supersaturation versus inhibitor can be determined for an individual, and that stone formers show greater supersaturation and less inhibition of crystalization and stone formation.

Matrix initiation - Matrix is a derivatives of several of mucoproteins of urine. Matrix content of a given stone varies, but most solid urinary calculi have a matrix content of about 3 percent of weight (Boyce and King[8] 1959) matrix may inhibit crystals growth interfere with crystal aggregation, and even enhance stone growth. At the present time the uromucoid of normal individuals is thought to be a beneficial inhibiter of crystalization and stone formation, where as the matrix of stone formers represents uromucoid with some qualitative defect that alters it's ability to inhibit crystal$ization or even causes it to promote stone formation (Finlayson[17] 1974).

Intranephronic and fixed nucleation :

Boyce and King[8], 1954 & Finlayson[17] 1974, These workers state that the major process that ultima-

tely leads to stone formation is aggregation of small crystals formed previously in the kidney. Some investigators believe that the initial nucleation and growth of nuclei and crystals begin in the renal tissue (Intranephronic), while other believe that the process begins freely in renal tubular urine. Intranephronic calculosis is probably most important in calcium stone disease.

Extranephronic and free particle nucleation

Proponents of extranephronic theory of urinary stone formation believe that it all happens in urine. Hence one possibility of matrix theory of stone formation is the fact that uromucoid normally acts as an inhibiter. Patient with stone disease may lack some significant component of uromucoid or produce additional components that decrease its inhibiting action.

Epitaxy : If a crystal has a pattern or organization of ions that is regular and predictable, this structure is called a latice. This surface latice may resemble very closely that of second best different type of crystal. Depending upon closeness of resemblance, the second type of crystal may actually be able to grow upon the surface of the first. Epitaxy required oriented overgrowth of one crystal on the surface of the another.

Final Theory :

This final theory of urolithiasis is an attempt to comprise all the elements discussed pre-

viously

1. Renal function must be adequate for the excretion of excess amount of crystallizable substance.
2. Kidney must be able to adjust it's pH excretion to confirm to that required to crystallize the substance.
3. Urine must have a complete or relative absence of a number of inhibitors of crystalization of the crystallizable components.
4. Crystal mass must reside in the urinary system for a time sufficient to allow growth or aggregation of crystal mass to a size large enough to obstruct the urinary passage through which it is proceeding. Hence stasis may have an important part in the genesis of urinary calculi.

RENAL/URETERIC COLIC

Bailey & Love's[6] (1988) Renal pain is usually dull ache situated mainly in the costovertebral angle, but also in the upper and outer quadrant of the abdomen. Renal pain, when localized is usually felt in the back of the loin with its maximum intensity in the renal angle i.e. that angle between the outer border of erector spinae and the twelth rib (Posterior renal pain).

It may also be felt over the front of the abdomen about one inch below the tip of the ninth costal cartilage (anterior renal pain). The pain is persistent and aching in character and is caused by stretching of the pelvis or capsule of the kidney. Sometimes

the patient feels pain in the opposite kidney which hypertrophies in order to compensate the impaired function of its fellow.

Renal or ureteric colic is due to violent contraction of the renal pelvis and ureter in order to expel a stone or blood clot. This is characterized by spasmodic pain that starts in the renal angle and radiates from the loin down to the groin, testis and inner side of the thigh i.e. along the distribution of the genitofemoral nerve, L_1 and L_2. As the obstructing agent comes down into bladder or falls back into the renal pelvis, the colicky pain passes off as suddenly as it came. (K. Das[29] 1990).

The pain of acute renal colic is usually severe and demands immediate and complete relief. The established mode of therpay are

a. Narcotic analgesic often combined with aspasmolytic agent. However side effects and the risk of drug addiction indicated the need for an alternatives to narcotics.
b. Non narcotics - analgesic- antispasmodic combination, Baralgan is widely used example of the second group. It is a combination of dipyrone, which is an analgesic a benzophenone components, which is a smooth muscle relaxant and a diphenyl derivatives, which has as a parasympatholytic action.

Recently, a third option has become available based on a better understanding of the physiolo-

gical changes during ureteral obstruction and colic. (Kill.F.[33], 1987).

This ureteric obstruction causes increased synthesis and release of prostaglandins. As a result renal pelvic pressure rises, causing renal colic. Prostaglandin inhibitor have been used to relieve the pain of renal colic. (Seharmn and Carlson[78] 1975).

Finally since prostaglandin acts as a intermediaries in pain transmission, impairment of prostaglandin synthesis may have a direct effect on pain perception. This striking effect may be explained by the reduction fof the rise in intrapelvic pressure mediated by the release of prostaglandin in the renal medulla during ureteric obstruction. Prostaglandins inhibitor have been used to relieve the pain of renal colic.

Out of many NSAIDs Diclofenac sodium, the sodium salt of o (2.6 Dicloraphenylamino) - Phenyl acetic acid is a non steroidal antiinflammatory drug a potent prostaglandins synthetase inhibiter has been reported to relieve renal colic more effectively than the previously used drugs. Drugs[63] 35 (1988).

PHARMACODYNAMIC PROPERTIES

Diclofenac is NSAI drugs with analgesic and antipyretic activity and is common with other aspirin like antiinflammatory drugs, it is potent inhibitor of

prostaglandin (PG) synthesis. It is phenylacetic acid derivative, (Sellmann[71], 1986) and it is extensively metabolised, but none of its metabolities posses significant pharmacological activity compared with other drugs which inhibit the prostaglandin synthesis (Maier[48] et al 1979; Menasse[54] et al, 1978).

Anti-inflammatory activity : Diclofenac is active in suppressing inflammation and oedema induced by carrageenan, (Krupp[38] et al 1975) mustard or croton oil. In addition, the drug also suppresses coton pelle granuloma formation (Doriett[14]o de menezes, 1985) and vascular permeability induced by human plaque in rats. Diclofenac also effective in reducing primary and secondary inflammation in adjuvent arthritis. In these tests the potency (Weight for weight) of diclofenac was similar to that of indomethacin, greater then that aspirin, buprofen, naproxen and phenylbutazone and less than that of piroxicam.

The anti inflammatory activity of diclofenac is not caused by stimulation of the hypothelimopitutary adrenocortical axis, as the effect is maintained in adventectomised rats (Krupp[38] et al 1975).

Analgesic activity - Diclofenac is an effective analgesic in rats and mice, inwhich it inhibits writhing induced by ethacrynic acid (Menasse[54] et al, 1978) acetic acid (Menasse[54] et al; 1978; Noguchei[57] et al, 1984 etc.) Phenylbenzoquinone (Menasse[52] et al 1978) and yeast. It is also effective in

raising threshold of agjuvant induced arthritic pain (Noguchol[57] et al, 1984). The potency of diclofenac in these tests was similar to that of indomethacin and piroxicam but greater than that of aspirin, ibuprofen, naproxen and phenyl butazone.

In a placebo-controlled double blind study (Stacher[75] et al, 1986), the analgesic activity of single oral doses of diclofenac 75 mg and 150 mg was compared with codeine 60 mg in relieving experimental pain induced by the electrical and thermal stimulation of skin in 48 healthy human subjects. Pain threshold values increased with all active treatment compared with placebo, dilcofenac 150 mg was more potent than codeine 60 mg. Which was in turn more potent than diclofenac 75 mg. Codeine produced more side effects than placebo and diclofenac, while diclofenac and placebo were similarly well tolerated.

Sacerdote[70] et al (1985) found that diclofenac 100 mg/kg administered to rats decreased pitutary B enderphine and increased hypothalmic concentration of the peptide. The same group of workers studied the effect of diclofenac 150 mg/day or placebo for 2 days in 8 patients with extracranial shunt (Martini[53] et al, 1984). Plasma Bendophin concentration were increased nearly four fold on diclofenac (P/ 0.025), while placebo had no effect. There were no changes in Bender-

phin and either serotonin or catecholamine metabolites in cerebrospinal fluids. The authors suggested that Bendorphins may contribute to the potent analgesic activity of diclofenac.

Antipyretic activity :- In rats with yeast induced fever the dose of diclofenac required to reduce body temperature by 1.5°c was less than with indomethocin, ibuprofen, Phenylbutazone, naproxen and aspirin (Menasse[54] et al, 1978).

Gastrointestinal effects:- Controlled studies in healthy subjects measuring faecal blood loss or using endoscopic examination show that diclofenac sodium causes less gastrointestinal damage than aspirin, feprazone or naproxen, but more than fenclofenac.

Osnes[59] et al (1979) found that diclofenac 100 mg/day caused significantly ($p < 0.02$) less gastritis and haemorrhagic and erosive lesions of the gastroduodenal mucosa than naproxen 500 mg/day in 14 subjects. Lethola and Sipponen[43] (1977) compared the gastric damage induced by diclofenac 75 mg/day and naproxen 500 mg/day in 6 subjects. Erosions tended to occur more frequently with naproxen, but too few subjects were enrolled for valid statistical analysis.

Several studies have measured faecal blood loss using the 51 Cr-labdlled erythrocyte technique Uthgenannt[81] (1981) reported faceal blood loss over a 3 weeks period totalling 32 ml to 174 ml in 8 subjects given aspirin 3 mg/day, 23 to 167 ml with naproxen 750mg/day and 19 to 39 ml with diclofenac 150 mg/day. In a one week

crossover study in 6 subjects (Uthgenannt[80], 1977), mean daily blood loss with naproxen 750 mg/day (4.9 ml) was greater than with diclofenac 150 mg/day (2.0 ml) or feprazone 800 mg/day (3.7 ml). In another one week crossover study in 6 subjects (Uthgenannt and Letzel[81], 1981) the mean increase in daily blood loss with diclofenac 150 mg/day (0.91 ml) was greater than with fenclofenac 1200 mg/day (0.74 ml) and 900 mg/day (0.56 ml).

To assess gastric irritation (Brendl[9] et al, 1983; Bruhn[10] et al 1982) by single oral dose of corpsofen 150 mg, diclofenac 50 mg and piroxicam 20 mg produced similar effect, indomethacin 50 mg and aspirin 500 mg caused significantly more irritation.

Effect on arachidonic acid metabolism

Diclofenac is a potent inhibitor of cyclooxygenase (Prostaglandin synthetase) in vitro, as measured by the worked reduction in synthesis of prostaglandin Prostacyclin and thromboxane products. At high concentrations in vitro diclofenac did not inhibit phospholipase A_2, which controls arachidonic acid formation from phospholipids and had negligible effects on the 5 and 15 lipoxygenase enzyme (Ku et al[39], 1985, 86). However these authors showed that formation from phospholipids from the lipnygenase pathway (Leucotrienes and 5 hydroxeicosat etreenoic acid) is reduced by high concentration of

diclofenac in vitro and exvivo in rates and human leucocytes, This seems to be caused by the decreased availability of intracellular arechidonic acid, [redacted], which result from enhensed reincorporation of this substrate into the tryglyceride pool. This effect on lipoxygenase in inflammatory products may contribute to the anti-inflammatory effect of diclofenac in vevo, but the formation of cyclo-oxygenase is probably the primary site of action.

In vivo, diclofenac decreased urinary PGF_2 and PGE_2 in rabbit renal medulla(Oliw[58] et al, 1978) and PGE_2, 6 keto -PGF_1 alpha and PGI_2 in the gastric mucosa of human.

Seppala[74] et al (1985) found that diclofenac 200 mg administered orally in divided doses over 1 day significantly ($P < 0.05$) reduced PGE_2 and thromboxane B_2 (by 50 - 60%) and tended to reduce 6 Keto PGI_{alpha} (by 30%) in the synovial fluids of patients with rheumatoid arthiritis. The effects of diclofenac were more pronounced than approximately equivalent therapeutic dosages of the other NSAIDs tested (aspirin, corprofen, indomethacin). Naproxen, proquazone and tolfenamic acid). The authors suggested that these agents which produced the best relief of acute pain in rheumatoid arthiritis w were the most potent inhibitors of prostaglandins in synovial fluid.

Raimann and Frolich[68] (1981) found that 24 hours urinary excretion of PGF_2 was decreased by about 50% when diclofenac 150 mg daily was administered to 5 healthy women for 7-10 days. This might effect prostaglandin dependent renal function such as natriuresis and lithuresis.

Effect on Renal function : A single oral dose of diclofenac 50 mg did not have any significant influence on uric acid excretion in 5 rheumatic patients with normal renal function (Tiitinen[79] et al 1983).

In a non-blind study Vandenburg[83] et al 1984) 62 elderly patients with osteoarthritis received diclofenac 75 mg/day or Sulindac 400 mg/day for 12 weeks. Mean blood urea increased ($P < 0.05$) from 7.63 to 9.17 mmol/L on diclofenac but was unchanged on sulindac. Clinically significant increases in blood urea nitrogen have been rarely reported during treatment with diclofenac.

Laurent[42] et al (1987) treated 29 patients with membroproliferative or IgA gloverulonephritis with diclofenac 100 mg/day or placebo in a randomised double blind study. Diclofenac produced a significantly greater median decrease in proteinuria after 2 months treatment compared with placebo (-70% - 6%) $P < 0.01$). Thus, while diclofenac exerted a short term antiproteinuria effect. It remains to determined weather it has any therapeutic value in affecting the final outcome of glomerulonephritis.

Other effects in brief

a) Carbohydrate metabolism - Diclofenac 150 mg/day had no adverse effect on blood glucose concentration or 24 hours urinary glucose excretion in 13 maturity onset diabetics treated with diet alone, or in another 14 maturity onset diabetics well controlled with diet and tolbutamide 500 -2000 mg/day (Schlumpf[73] 1978). Oral administration of diclofenac 50 mg to 6 healthy subjects did not affect blood glucose concentration, plasma free fatty acids concentration increased about 0.5 to 0.9 mmol/L ($p < 0.05$).

b) Platelet aggregation - In common with other NSAIDs, diclofenac is a potent inhibitor of the secondary phase of human platelet aggregation in vitro (Jehin and Gagnon[27] 1971). At low concentration the drug inhibits secondary aggregation by ADP and adrenaline, and aggregation with collagen.

c) Hormones :- Administration of SR diclofenac 100 mg/day for 22 days to 10 rheumatic patients had no significant effect on plasma kallikrein concentration. However, mean urinary excretion of kallikrein was reduced to about one half of the control value after 15 days, which was not statistically significant and recovered after another week (Gross[21] et al, 1984). Mean plasma renin activity and aldosterone were reduced to 61.6% and 68% of control value respectively, after administration of diclofenac 150 mg/day to 20 healthy subjects for 3 days.

Leucocyte function : While NSAIDs are thought to exert their effects mainly by inhibiting prostaglandin synthesis. It has also been postulated that they inhibit a number of leucocyte responses such as lysosomal enzyme release and superoxide production (Friman[18] et al 1986). which appear to play a role in the pathogenesis of rehumatic disease and in the degradation of connective tissue and joints.

Pharmacokinetic properties (Brief):- Diclofenac is rapidly and efficiently absorbed after conventional oral rectal or intramuscular administration. After intramuscular administration peak plasma concentration are attained after 10-30 minutes. With the enteric coated formulation peak concentrations are reached after 1.3 to 2.5 hours and this is delayed by food to 2.5 to 12 hours. After a single 50 mg dose of these formulations, mean peak plasma concentration of unchanged diclofenac are 0.7 to 1.5 mg/L. No clear peak concentration are found after a single 100 mg dose of sustained release diclofenac, although mean concentration was about 0.1 mg/L at 2 hours. Peak plasma concentrations and area under the plasma concentration time curve are linearly related to dose over the range of 25 to 150 mg regardless of administration routes, and no accumulation occurs after repeated doses. (John[28] 1979; Kendall[31] et al 1979; Geiger[20] et al, 1975, Willis[86] et al, 1979).

Like other NSAIDs, diclofenac is highly (7/ 99.5%) protein bound. The mean total volume of distribution is .12 to .17 L/Kg and that of central compartment is .04 L/Kg. The drug efficiently penetrates inflammed synovial fluid where high concentrations are maintained compared with plasma concentrations. Diclofenac and its metabolites cross the placenta in animals, and small amounts may be found in the breast milk of women (Riess[69] et al, 1978; Chamouard[13] et al, 1985; Wanger and Sule[85] 1979; Aylward[3] et al, 1980; Benson[5] et al 1985; Liaw[44] et al, 1985; etc.).

Diclofenac undergoes significant first pass metabolism and only 60% of the drug reaches systemic circulation unchanged following oral administration. It is eliminated principally by hepatic metabolism and subsequent urinary and biliary excretion of glucuronide and sulphate conjugates of the metabolites. The principle metabolite in human is 4 hydroxydiclofenac, which possess negligible anti-inflammatory activity compared with the parent drug; the amount excreted in urine accounts for 20-30% of the dose and that in bile for 10-20%. The mean elimination half life after a radio-labelled dose is about 30 hours for the tracer.

Age and renal or hepatic impairment do not appear to have any significant effect on plasma

concentration of unchanged diclofenac, although metabolite concentrations may be increased by severe renal impairment.

Stierlin[76] et al, 1979; Willis[86] et al 1979; Kendall[31] et al, 1979; Menasse[54] et al, 1978; etc.)

THERAPEUTIC USE IN RENAL COLIC : Prostaglandin are implicated in the aetiology of renal and billary colic, and it was hypothesised that an effective treatment might be provided with prostaglandin synthetase inhibitors. Among them intramuscular diclofenac has been found to provide rapid and effective relief of pain (Kantor[30] 1986; Kral[37] 1985).

Preliminary non-comperative studies indicated that single intramuscular dose of diclofenac 25 to 75 mg were effective in renal (Naveh[56] 1982) and biliary colic (Lundstam[40] et al, 1983) In subsequent comparative studies intramuscular diclofenac 50 mg and, more often, 75 mg employed. Diclofenac was clinically effective compared with placebo. Onset of analgesia occured within 15 minutes and was maximum with in 30 minutes. No decline in analgesia occured until 4 hours after injection. In responders complete analgesia occured in most patients treated with diclofenac, while few of those on placebo also had a complete response.

Diclofenac 50 to 75 mg was superior in efficacy both statistically and clinically, to many narcotics and spasmolytic combinations, although similar efficacy was found to indomethacin (Comeri et al 1984) and pentazocine (30 mg Cuilez[64] et al 1984). In a non blind study (Sami Khalife[72], 1986) Intramuscular diclofenac 50 mg and as intravenous combination of pethidine 50 to 100 mg plus hyoscine butylbromide 20mg were effective in 90% and 97% of patients, respectively.

Side effects : Diclofenac rarely produced any side effects, but minor, although statistically significant, reduction in blood pressure and heart rate occured in some studies (Grossi[22] et al, 1986; Lundstam[40] et al, 1982, 1985, 1987). However, diclofenac rarely produced the frequent limiting CNS effects (Nausea, vomiting, dizziness, sweating, euphoria) associated with narcotic analgesics which were often cited as a limiting factor in narcotic use even when they demonstrated similar efficacy to diclofenac (Cuitez[64] et al, 1984; Sami Khalife and Sharkewi[72] 1986).

Following is the summary of results of randomised double blind clinical trials compering single intramuscular doses of diclofenac with placebo, narcotic, analgesics and spasmolytic agent in patient with renal colic.

Reference	Dose (No. of patients	Response rate (%)
Lundstam et al [40] (1980)	Diclofenac 75 mg (9)	100
	Placebo (10)	30
Lundstam et al [40] (1982)	Diclofenac 50 mg (34)	91
	Spasmofen (32)	63
Comeri et al [12] (1984)	Diclofenac 75 mg (27)	74
	Indomethacin 50mg (24)	79
	Noramidopyrine 1 g+ Pitofenone .4 mg + Fenpiverine .04 mg (24)	42
Neveh et al [56] (1984)	Diclofenac 75mg (19)	84
	Papaverine 80mg (13)	24
Cuitez et al [64] (1984)	Diclofenac 75 mg (24)	78
	Hyoscine butylbromide 20mg (23)	26
	Pentazocine 30 mg (14)	79
Hetherington & Philip [26] (1986)	Diclofenac 75 mg (24)	93
	Pethidine (28)	65

MEASUREMENT OF PAIN

Huskisson[23] (1974) of the various methods for measuring pain the visual analogue scale seems to be the most senstive. For assessing response to treatment a pain relief scale has advantages over a pain scale. Pain can not be said to have been relieved unless pain or pain relief has been directly measured.

ScaleA(Simple descriptive pain scale): Keele[34] (1948) described a four points scale. grading pain as slight, moderete, severe and agonising. Agonising pain is rare, and this grade has been dropped by most subsequent usuers of the scale. The term "mild" is often used instead of "slight". A patient with slight pain has only one possible grade of improvement complete relief, which is seldom achieved by simple analgesics in chronic pain. (So in this study we used only moderate and severe pain) because in this study any patient has not been found of mild pain.

Hewer et al[24] (1949) used this scale to measure the effects of narcotics analgesics, and it remain a useful standard method with the advantage of simplicity. The disadvantage of the method is its lack of senstivity (Huskisson[23] 1970).

The external distress manifested by the patient was graded by the assessor on a scale 1 to 4, 1

represented a patient who was absolutely comfortable while 4 ment a patient who appeared severely distressed. Scale B (visual analogue scale): some of the problem of the simple descriptive pain scale can be overcome by using either a visual analgue or the graphic rating method. Clarke and spear (1964) used a visual analogue scale to measure well-being, and concluded that it was both reliable and senstive, though it is difficult to establish reliability in repeated measurements of subjective states, that is no reson to expect that pain would remain constant even from one minute to the next.

Freyed (1923) patients find simple descriptive pain scale easier than visual analogue pain scale. Berry and Huskisson[23] (1972) described that all patient were able to complete a simple descriptive pain scale, 7% were unable to complete visual analogue scale on the first occasion after a single adequate explanation of the method, and 3% were unable to complete graphic rating scale. Patients may require painstaking explanation from a trained assistant, especially on the first few occasions.

This scale has not been included in our study because of the fact that most of the patients coming to our M.L.B. Medical College Hospital, Jhansi belong to rural background and Bundelkhand being a backward area of the state.

scale C (Pain relief Scale):- charted relief of pain An analogue scale was used in which the patient expressed relief of pain in terms of "Annas-in-rupee". Thus percentage of relief of pain was charted on scale as a fraction e.g. 2/16, 4/16, 8/16 ett.

(SHAH et al[66] 1986)

Criteria of relief :-

Result were assessed as per the following criteria.

1. Onset of action :- Time taken to achieve 25% relief i.e. 4/16 on scale C. The moment of starting the injection of the drug is considered as zerotime.
2. Adequate

Complete relief :- was said to have occured only if an when the patient reached a score of 1 or 2 on scale A (i.e. Nil/Mild discomfort) and had relief of atleast 14/16 on scale C (i.e. 90% relief with only minimal residual soreness and had no colic at all.

3. Partial relief : Mild persistant colic or significant residual soreness at 30 minutes (i.e. score 3 on scale A and relief of not more than 12/16 on scale C was rated as partial relief only.

MATERIAL AND METHOD

MATERIAL AND METHOD

The present study was done from April, 1990 to April, 1991 in the department of Surgery, M.L.B. Medical College Hospital, Jhansi (U.P.). It comprised three hundred twenty five (325) patients of all age groups and both sexes, who had clinically proved renal/ureteric colic. All those cases who could not be completely assessed have been excluded from the study.

The present study was conducted with the following objectives:

1. Clinico-pathological study of renal colic patients based on clinical finding and urine analysis etc.
2. To evaluate the diclofenac sodium as a analgesic in acute renal colic.

METHOD

1. HISTORY : A detailed history was taken regarding following points :
   a. Age : Age of the patient at the time of admission was noted and patient were kept in six age groups :- 6-14, 15-25, 26-35, 36-45 and 46-55.
   b. Sex : Patients were kept in two groups i.e. male and female.

c. Religion: Patient were kept in two groups according to their religion Hindu and non Hindu.

d. Occupation: Exact occupation of each patient was noted and patients were kept in three categories; highly active moderately active and sedentary. Highly active group included Farmers and Labourers etc. Moderately active group included students, house wifes, service persons and children, sedentary group included excecutive class persons and elederly persons.

ec. Socio-economic status : Socio economic status of each patient was decided as per capita income of his family. Per capita income was calculated by dividing total Family income with number of family members. There are five classes based on per capita income per month. Class I 7 Rs. 600/- , Class II Rs. 590/- to Rs. 300/-, Class III Rs. 299/- to Rs. 140/- Class IV Rs. 139/- to Rs. 60/- and Class V 7 Rs. 60/-

We grouped the patients in three categories i.e. High socio-economic status (Class I) Middle socio-economic status (Class II + Class III) and low socio-economic status Class (IV & V) category.

f. Marital status:- Patient were kpet in two groups i.e. married and unmarried.

g. Complaints :- Following chief complaints have been noted along with their duration. Patient were kept in Four groups according to their duration of symptoms; $\angle$ 1 months, $\angle$ 2 months, $\angle$ 3 months and γ 3 months.

A. Pain :- Following points were asked in relation to pain :-

i. Duration : exact duration of pain was noted.

ii. Time of occurance: Exact time of pain was noted.

iii. Nature : Wheather pain was constant or intermittent in nature with periods of remission, was noted.

iv. Frequency: numbers of occurance of same type of pain was noted.

v. Radiation: Radiation ofpain if any, to other point was noted, and any referred pain was also noted.

vi. Character: Character of pain, it being

burning, penetrating, cutting or dullach was also noted.

vii. Relationship of pain with meal, posture and movement was also noted.

B. Vomiting/Nausea :- Those cases in which nausea/ vomiting associated with pain its number, amount of vomitus, colour of vomitus and effect of vomiting over pain was noted.(increased or decreased).

C. Burning during micturition :- Following points were noted in relation to burning during micturition.

i. Duration : Duration of burning during micturition and whether it preceeded or followed the pain was asked for and noted.

ii. Severity : Severity of burning during micturition and its occurance during exact point of micturition was noted.

D. Retention of urine :- If there was retention/inhibition of urine due to pain or burning during micturition, was also noted.

E. Change in colour of urine :- Following points, were noted under this headings :-

1) Colour of urine Exact colour of urine passed, was noted: bright red or smoky (Haematuria), opaque (Chyluria) or hazy (Pyuria).

ii) Time of occurance : Maximum change, in the colour of urine was noted during which part of micturition.

iii) Frequency : Number of occurance of change in the colour of urine and whether it was associated with pain, fever or consumption of fatty meals, was noted.

F. Past History :- Past history of passage of stone per urethra, other urinary stones, same type of attacks in the past, prolonged period of immobilization, any other chronic illness like diabetes, hypertension, tuberculosis, gout etc., were noted.

1) Treatment history - Any treatment taken in past was noted. Specially those who had been given analgesics 6 hours before admission were excluded in this study.

G. Family History :- Family history of urelithiasis, gout or tuberculosis was noted.

H. Personal history :- Personal history of smoking and alcoholic consumption was noted and patient were divided into smoker and non smoker and alcoholic and non alcoholic respec-tively.

I. Dietary habits :- Dietary habits of patients were also noted with special reference to exact type of food consumed, consumption of tea, coffe, fruit juices, cola and amount of water consumed. Patient were kept in four

categories; purely vegetarians included patients who only eat vegetarian diet like Dal, green leafy, tomates, milk and milk products; predominantly vegetarian included those patients who occasionally eat non vegetarian diet like meat, fish, chicken etc. Purely non vegetarians included those patient who only eat fish, meat etc. Predominantly non-vegetarians, included those patient, who predominantly eat meat, fish etc.

2. Physical Examinations :- Stress was given specially to the examination of abdomen, with special reference to any lump in the lumber region, fullness and tenderness in renal angle and examination of external genitalia.

3. Investigations :- Following investigations were done: TLC, DLC, Hb, Blood sugar and Blood urea were done.

b. Urine :- Albumin, sugar, microscopic examination for casts, crystals, R.B.C. puscells and epithelial cells was done.

c. Radiological

i. Plain X-ray KUB was done in all cases to see the site and size of stone or if there is no radio opaque shadow in clinically diagnosed cases.

Patient were kept in four groups on the basis of site of stone; patient with stone above the ureter (pelvis and kidney), patient with stones in upper 1/3 of ureter (up to lower border of L_3 vertebra), patient with stone in middle 1/3 of ureter (from lower border of L_3 vertebra to lower border of sacroiliac joint) and patient with stones in lower 1/3 of ureter (from lower border of sacroiliac joint) to uretero-vesical junction.

ii. I.V.U: Intrevenous urography was done to see the functions of Kidney and to see radiolucent stones.

General Examinations:

B.P., Pulse rate and respiratery rate were noted at the time of admission.

Treatment and progress:

Treatment plan of these patients was as follows:-

i. All patient were admitted to emergency or surgery ward with acute renal/ureteric colic, included in study group.

ii. The diagnosis was confirmed by the clinical signs and symptoms.

iii. Patient who fulfilled the clinical criteria of acute renal/ureteric colic were allocated to treatment with intramuscular injection of 1 ampoule of diclfenac sodium (Dicloran 3 ml, 75 mg).

iv. Patient with a history of allergy, asthma, bleeding disorder, peptic ulceration, women in pregnancy and those who had been given analgesics 6 hours before admission were excluded.

Methodology

After preliminary examination and recording of B.P. Pulse rate, the pain was assessed by scale A (Keele[34], 1948), as a mild, moderate or severe. The dicloren injection was then given intramuscularly (deep gluteal region) over a period of not less than one minute. On completion of the injection, the analgesic effects of injection dicloren was assessed after 15 and 30 minutes after the injection and evaluated the patient relief in pain as per scale C (R.S.[66] Shah, 1986), and it was noted as " no effect ", " partial relief " or " complete relief ". At the end of 30 minutes of injection B.P. (Systolic/Diastolic), and pulse was again recorded. The patient was also asked if he/she experienced drowsiness, nausee, vomiting, dry mouth or any other side effects and they were similarly recorded.

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OBSERVATIONS

OBSERVATIONS

These observations were made on patients (325) who were diagnosed as suffering from acute renal/ureteric colic and admitted in hospital irrespective of age, sex, religion, socio economic status, occupation etc. coming to M.L.B. Medical College, Hospital, Jhansi between April, 1990 to April, 1991.

TABLE NO. 1

Cases of Acute Renal/ureteric colic related to total hospital admissions.

Total hospital admissions	Cases of ureteric colic	Percentage in relation to hospital admissions
26070	720	2.77%

Above table shows:-

1. 2.77% of hospital admissions are of acute renal/ureteric colic cases.

TABLE NO. 2

Incidence of acute renal/ureteric colic by sex.

Total number of cases	Males	Percentage of males	Female	Percentage of females
325	243	75%	82	25%

Above table shows:-

1. Male :Female ratio of acute renal/ureteric colic is 3:1.

TABLE NO. 3

Incidence of Acute renal/ureteric colic by age.

Age groups	No. of patients	Male	Percentage of males	Female	Percentage of females	Total
6 -14	6	5	1.54	1	.31	1.85
15-25	118	86	25.70	32	9.84	35.54
26-35	148	104	32	44	13.54	45.54
36-45	35	30	9.23	5	1.54	10.77
46-55	18	18	5.54	-	-	5.54
Total	325	243	74.71	82	25.23	app. 100.00

Above table shows:-

1. Maximum incidence of ureteric colic is in the age group 15-35 years (81.08%).
2. No cases of ureteric colic found below 5 years and above 55 years.
3. Minimum incidence of ureteric colic is in age of 6 - 14 years.

TABLE NO. 4

Incidence of Acute renal/ureteric colic by religion.

Religion	Number of patients	Percentage of patients
Hindu	286	88%
Muslim	23	7.07%
Others	16	4.92%

Above table shows:-

1. Maximum incidence of ureteric colic among Hindus (88%).

TABLE NO. 5

Incidence of acute renal/ureteric colic by occupation.

Type of occupation	Number of patient	Percentage of patients
Highly active	173	53.26%
Moderately active	128	39.36%
Sedentary	24	7.38%

Above table shows:-

1. Incidence of ureteric colic is highest (53.26%) in highly active patients i.e. Labourers, Farmers etc.
2. Incidence of ureteric colic is lowest in sedentary patients i.e. elderly people and executive class persons.

TABLE NO. 6

Incidence of acute renal/ureteric colic in relation to socio economic status.

Socio economic status	No. of patients	Percentage of patients
Low	32	9.84%
Middle	196	60.28%
High	97	29.84%

Above table shows:-

1. Incidence of ureteric colic is highest in middle class patient (60.28%).
2. Incidence of ureteric colic is lowest in low class patient (9.84%).

TABLE NO. 7

Incidence of acute renal/ureteric colic in relation to dietary habits.

Dietary habit	Number of cases	Percentage of patients
Pure vegetarian	88	27.04%
Pre-dominantly vegeterian	202	62.12%
Pure non-vegetarian	-	-
Pre-dominantly non-vegetarian	35	10.76%

Above table shows:-

1. Incidence of ureteric colic is maximum in predominantly vegeterian (62.12%).
2. No patient in our series was pure- non-vegetarian.

TABLE NO. 8

Incidence of Acute renal /ureteric colic in relation to alcohal consumption.

Type of patient	Number of patients	Percentage of patients
Alcoholic	68	20.92%
Non-alcoholic	257	79.08%

Above table shows:-

1. Ureteric colic are less common in persons consuming alcohal (20.92%).
2. Ureteric colic are more common in person not consuming alcohal (79.08%).

TABLE NO. 9

Incidence of various symptoms at the time of admission

Symptoms	Number of patients	Percentage of patients
Pain	325	100%
Haematuria	71	21.84%
Burning micturition	161	49.56%
Retention of urine	2	.60%
Lump	1	.28%

Above table shows:-

1. Pain was the commonest symptom at the time of admission. It was present in all cases (100%).
2. Burning micturition was next common complaints (49.56%).

TABLE NO. 10

Microscopical examination of urine in clinically diagnosed acute renal/ureteric colic cases.

Microscopical examination of urine	Number of patients	Percentage of patients
Pus cells	71	21.85%
R.B.C.	132	40.92%
Epithelial cells	62	19.22%
Crystals/cast	32	9.92%
Within normal limits	146	45.26%

Above table shows :-

1. Incidence of abnormal number RBC is maximum 40.92% in urine.
2. Incidence of crystals is lowest in all cases.

TABLE NO. 11

Incidence of radio opaque shadow (stone).

Number of patient clinically diagnosed as acute renal/ ureteric colic	Number of patients in whom radio-opaque shadow present (suggestive of stone)		Number of patients in whom no radio-opaque shadow seen	
	No.	%	No.	%
325	130	40%	195	60.45%

Above table shows:-

1. No radio-opaque shadow is present in 60.45% of cases.
2. Incidence of radio-opaque shadow is present in 40% cases.

TABLE NO. 12

Incidence of acute renal/ureteric stone in relation to site.

Site of stone	Number of patients	Percentage of patients
Kidney + P.U.J.	55	42.30%
Upper one third of ureter	27	20.77%
Middle one third of ureter	16	12.31%
Lower one third of ureter	32	24.62%

Above table shows:-

1. Incidence of ureteric stone is maximum 75(57.70%).
2. Incidence of ureteric stone is minimum in middle one third of ureter 16(12.31%).

TABLE NO. 13

Incidence of stone in relation to side.

Number of patients	Side	Number of patients	Percentage of patients
130	Right	94	72.31%
	Left	36	27.70%

Above table shows:-
1. Incidence of stone is more on right side 94(72.31%).
2. Ratio of right : left is 3:1 approximately.

TABLE NO. 14

Incidence of positive intravenous pyelography.

Number of patient	Number of patients in whom I.V.P.done	Patient with positive findings due to stone		Patient with negative I.V.P.	
		No.	Percentage	No.	Percentage
325	92	82	89.13%	10	10.86%

Above table shows:-
1. No positive finding is present in 10(10.86%) cases.

TABLE NO. 15

Division of patient according to degree of pain.

Number of patient	Mild	Moderate Pain		Severe pain	
		No.of cases	Percentage	No.of cases	Percentage
325	0	152	46.76%	173	53.24%

Above table shows:-
1. Incidence of severe pain is maximum 53.24%.
2. Incidence of mild pain is not present in our series of study.

TABLE NO. 16

Effect of Diclofenac injection on patients having moderate pain after 15 minutes and 30 minutes.

Number of patient	Nature of effect	Number of patient response after 15 minutes	Per-centage	Number of patient response after 30 minutes	Per-centage.
152	Complete relief	62	40.79%	131	86.22%
	Partial relief	90	59.21%	21	13.88%

Table shows:-

1. Incidence of partial relief is maximum after 15 minutes 59.21%.
2. Incidence of complete relief is maximum after 30 minutes of injection 86.22%.
3. Incidence of no effect (response) after 15 and 30 minutes is not present in our series of study.

TABLE NO. 17

Effect of Diclofenac injection on patients having severe pain after 15 and 30 minutes.

Number of patient	Nature of effect	Number of patient response after 15 minutes	Percentage	Number of patient response after 30 minutes	Percentage.
173	Complete relief	156	90.17%	162	93.55%
	Partial relief	17	9.83%	11	6.45%

Above table shows:-

1. Incidence of complete relief after 15 and 30 minutes are 90.17% and 93.55% respectively.
2. Incidence of partial relief after 30 minutes lowest 6.45%.
3. Incidence of " No effect" after 15 and 30 minutes is not present in our series of study.

TABLE NO. 18

Blood pressure and pulse rate assessment before and 30 minutes after treatment with diclofenac sodium injection in patients having moderate pain (Mean±S.D.).

Number of patient	Vitals	Before injection	After injection
152	Systolic blood pressure	134.26±8.20	122.31±8.20
	Diastolic blood pressure	92.56±5.50	87.58±5.50
	Pulse rate/mt.	74.39±4.95	70.84±4.95
	P < 0.001	P < 0.001	P < 0.001

Above table shows:-

1. Incidence of significant fall in systolic/diastolic, as well as pulse rate was found after 30 minutes of diclofenac sodium injection.

TABLE NO. 19

Blood pressure and pulse rate assessment before and 30 minutes after treatment with diclofenac sodium injection in patients having severe pain (Mean±S.D.).

Number of patient	Vitals	Before injection	After injection
173	Systolic blood pressure	145.68±10.61	128.31±10.61
	Diastolic blood pressure	95.10±7.16	87 ±7.16
	Pulse rate/mt.	77.58±6.27	70.52±6.27
	P < 0.001	P < 0.001	P < 0.001

Above table shows:-

1. Incidence of significant fall in systolic /distolic as well as pulse rate was found after 30 minutes of diclofenac sodium injection.

TABLE NO. 20

Relationship between vitals in different groups after 30 minutes of injection.

Vitals	Moderate pain		Difference	Severe pain		Difference
	Before	After		Before	After	
Systolic blood pressure	134.26±5.20	122.31±8.20	11.95±8.20	145.68±10.61	128.31±10.61	17.37±10.61
Diastolic blood pressure	92.56±5.50	87.58±5.50	4.98±5.50	95.10±7.16	87 ±7.16	8.1±7.16
Pulse rate/mt.	74.39±4.95	70.84±4.95	3.55±4.95	77.58±6.27	70.52±6.27	7.06±6.87

Above table shows:-

1. Incidence of significant fall of systolic, diastolic blood pressure as well as pulse rate in both type of pain, but more in case of severe pain.

TABLE NO. 21

Summary of adverse reactions in 325 patient treated with Diclofenac sodium (Dicloran) injection.

Number of patient	Side effects	After injection (within 30 minutes)	Percentage
325	Nausea	7	2.15%
	Vomiting	9	2.76%
	Diarrhoea	-	-
	Drowsiness	13	4.03%
	Dry mouth	3	.93%
	Any other	-	-

Above table shows:-

1. Incidence of drowsiness is maximum 4.03%.
2. Incidence of dry mouth is minimum .93%.

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DISCUSSION

DISCUSSION

Acute renal/ureteric colic is fairly common problem in Bundelkhand region. Although urolithiasis is known for more than 7,000 years, little attention was directed to localization of stones or to the cause of its formation. It was only during last few years that attention has been paid to understand the cause of colic in stone diseases.

Though stones in kidney and bladder may remain asymptomatic, ureteric and kidney stones cause recurrent attacks of severe pain to the patients and may ultimately lead to damage of kidney due to stasis and infection.

Our present work is a clinicopathological study on three hundred twenty five (325) cases of acute renal/ureteric colic. An attempt has been made to evaluate the analgesic effects of intremuscular administration of Diclofenac sodium (Dicloran) injection on acute renal/ureteric colic.

Incidence : Approximately we had 26070 admissions (from April 1990 to April 1991) in this hospital and out of this 720 patients were of acute renal/ureteric colic (2.77%). However number of cases compiled for study were three hundred twenty five out of total seven hundred twenty (720) cases of ureteric colic. The rest

of the cases were excluded either because of incomptetion of the study or due to non coperation of the patients.

Sex : It is a well known fact acute renal/ureteric colic are more common in males than in females, ratio being 3:1 (George W.Drach; Black [7] lock, 1969 (6). This facts has also been established in our study of three hundred twenty five (325) patient. We have also the same ratio with male preponderance (243 males and 82 females). Perhpps female hormones affect the ureter in such a way as to prevent stones from lodging there.

Age: Acute renal/ureteric colic is more common in between 15-35 years of age. We did not find any case below 5 years of age or above 55 years of age. Burkland and Rosenberg[65], 1955 (62); Prince and Seardind[61], 1960(59) have reported the maximum incidence between 30-50 years of age.

Relision : Though we have observed that Hindus predominate in our series (286-88%). This could be because of their dietary habits i.e. more consumption of milk and milk products, green leafy vegetables, tomatoes etc. or It may be general reflection of the population ratio.

Occupation : Hard work by manual labourers is associated with greater loss of water from body and leads to passage of highly concentrated urine, which may be responsible for its higher incidence in labourers. This fact has also been observed in our study (53.26%).

Socio-economic status : It is a well established fact that ur eteric colic is commonest among the poorly nourished people, There is some evidence that it is a deficiency disease. However as patients of middle socio-economic class attend more for institutional therapy, more cases have been reported in our study (60.28%). Anderson[2], in 1972 (2) reported that ureteric colic are more common in persons of lower and upper middle socio-economic class.

Diet : It has been observed in this series that vegetarians predominate (62.12%) vegetarian diet may be containing some crystalloid substances, which precipitate in concentrated urine.

Alcohal : No definite role of alcohal has been established so far, but we feel that alcohal causes diuresis and may be helpful in spontaneous expulsion of small stones. Only 20.92% of the cases in our series were alcohal consumers.

Ingestion of excessive amount of food stuffs, which contain high amount of purines (meat, fish) oxalates (green leafy vegetables and tomatoes) and calcium (Milk and milk products) may lead to increase in excretion of these substances in urine, which in turn may lead to increase in incidence of urinary stones as well as ureteric colic.

Symptoms : There are three common symptoms in our series of study. Pain is the commonest symptoms present in all cases (100%). It is well known that renal colic arises from the kidney associated with the inflammation or obstruction at the pelviureteric junction or in ureter. This ureteric obstruction causes increased synthesis and release of prostaglandins. As a result renal pelvic pressure rises, causing renal colic. (Lundstam and Wahlander) (40).

Clinically haematuria is present in only seventy one patients (21.84%). Stones are of importance when they obstruct urinary flow or produced ulceration and bleeding. That bleeding originates from the lesions which cause erosions or disruption of blood vessels or from inflammatory changes which in turn lead to erosion and diapedisis of red cells.

Burning during micturition is present in one hundred and sixty one patients (49.56%). Infection

favours the formation of urinary calculi. Both clinical and experimental data suggest that formation is common when the urine is infected with urea splitting streptococcus, staphylococcus or proteus. The predominant bacteria found in the nuclei of urinary calculi are a staphylococcus and Esch. Coli. The stones also predispose to superimposed infection, both by their obstructive nature, and by the trauma they produce.

Microscopical examination of urine : It is well known that infection favours the formation of urinary calculi In our series pus cells were present in seventy one (71) patients (21.85%). The stone is also liable to be cause of secondary infection both by their obstructive nature and by the trauma they produce.

Red blood cells present in one hundred and thirty two patients (40.92%). Stones cause the obstruction which further leads to ulceration and bleeding, that bleeding originates from the erosions or the inflammatory changes caused by stones due to trauma. (■■). Out of the total three hundred twenty five patients, in 146 patients (45.26%) urine examination was reported to be normal.

Radiological features

1. Plain X-ray (KUB) : Plain X-ray KUB was done in all cases who were diagnosed clinically as having acute renal/ ureteric colic. We have observed that only in 40% cases

radio-opaque shadow suggestive of stone was found and 60% X-ray have no radio-opaque shadow. Probable explanation is either stones are too small in size, that they could not be visualized in plain X-ray or the patient's abdomen was not prepared properly before X-ray or the stone could be radioluscent.

2. Site of stones : We have observed that ureteric stones are most common in lower one third (24.62%) of ureter, Mikkleson[41] et al (■■) also reported in 1966 that stones are more common in lower half (62.5%) in their study of 24 patients.

3. Side of stones : Renal /ureteric stones should occur with same frequency on both sides, but we have observed that they are more common on right side, the cause of which could not be ascertained (72.31%).

4. I.V.P. : Out of three hundred and twenty five patients ninty two patients in whom I.V.P. was done. No abnormality was found in 10 cases (10.86%). The rest 89.14% cases had either non visualized /poorely visualized. Kidney on the side of pain or had shown hydronephrosis/hydroureter or both.

Severity of pain : Out of total number of three hundred and twenty five patients, hundred fity two (152) that is about 46.76%, were having moderate pain where as one hundred and seventy three (173) of them that is about

53.24% were suffering from severe pain. No patient reported mild degree of pain in our study.

The experimental studies of Kill F (33) documented the physiological changes occuring during ureteric obstruction. Abe et al and Schramm and Carlson studied the release of prostaglandins during ureteric obstruction. These studies suggest the following sequence of events in ureteral obstruction.

1. Renal pelvic distention
2. Release of PGE_2 from renal medulla
3. Causes diuresis
4. Increase pelvic distention and pain

Use of prostaglandin inhibitors for relief of pain: Prostaglandin inhibitors act possibly through following effects to releive the pain in Renal/ureteric colic.

1. Block release of PGE_2
2. Reverse the diuretic effect
3. Reduce renal pelvic distention

Effect of diclofenac sodium (Inj.Dicloran) after 15 and 30 minutes of injection, on pain :

A. Moderate Pain group : The hundred and fifty two (152) patients of moderate pain group were given inj. diclofenac sodium intramuscularly deep in the gluteal region and the response to it was noted after 15 minutes and 30 minutes of the injection respectively. Complete relief was found in sixty two patients (40.79%) after

15 minutes. Where as partial relief was experienced by the rest ninty patients (59.21%). There was no patient who did not report relief. The number of patients experiencing complete relief at the end of 30 minutes rose to hundred and thirty one (131) where as partial relief was reported by remaining twenty one (21) patients. Not even a single patient reported abscence of response after 15 minutes and 30 minutes of the injection.

B. Severe pain group : Complete relief in colic was reported by 156 (90.17%) patients out of 173 complaining of severe pain, after 15 minutes of the given injection, where as 17 (9.38%) reported partial relief in pain at the end of same time. After 30 minutes the number of patients reporting complete relief rose to hundred and sixty two (93.55%) where as only eleven were left with partial relief. No patient reported absence of effect of the drug.

The superlative number of the patients having complete relief after the first 15 minutes of the given injection in severe pain category of 156 in comparison to the moderate type sixty two was note worthy. Lundstam, Wahlander (40) and others in their study regarding "prostaglandin synthetase inhibiter with diclofenac sodium of treatment of acute renal/ureteric colic" have reported partial or complete relief of pain within 30 minutes of injection in 31 out of 34 patients they studied.

R.Mirrales, J. Cami [67] (■) and others (1987) in their study " Diclofenac versus dipyrone in acute renal colic" have reported that no difference were found between the groups in terms of satisfactory relief of pain (7/ 50% improvement in initial pain), which was achieved in 22 of 27 diclofenac treated patients (81.4%), and in 15 of 27 dipyrone treated patients (65.2%). In order to study the extent of improvement in pain intensity, pain reting 30 minutes after drug administration, reported that diclofenac was better than dipyrone in terms of improvement in pain intensity and the proportion of patients obtaining complete relief of pain at 30 minutes, but there was no difference between the drugs in terms of satisfactory relief of pain.

In another study of Mr. Hetherington [26] (26) "diclofenac sodium versus pethidine in acute renal colic" showed satisfactory relief of pain after a single shot within 30 minutes of injection in 28 (93%) out of 30 patients studied.

Our present study shows that intramuscular injection of a compound that inhibit prostaglandin synthesis is remarkably effective in treating attacks of renal/ureteric colic. Renal colic is caused by tension in the wall of renal pelvis due to rise in pressure above the ureteric obstruction. This elevation of pressure in renal pelvis stimulates.prostlandin synthesis, which increases diuresis, causing a further

is thus to counteract the increased synthesis and release of prostaglandins, which are of pathogenetic importance in this condition.

Blood Pressure and pulse rate

Noticeable decrease was found in both systolic and diastolic blood pressure and pulse rate after 30 minutes of injection in both moderate and severe pain category. The variation was more marked in the severe pain category in blood pressure and pulse rate as well.

The difference between the systolic blood pressure in moderate pain was on an average 11.95 mmHg with 8.20 as standard deviation where as in severe pain category the difference was 17.37 mmHg with 10.61 as the standard deviation. The difference in diastolic blood pressure was 4.98 mmHg and 8.10 mmHg in moderate and severe pain category respectively with 5.50 and 7.16 as the standard deviation in the same sequence. The difference in pulse rate per minute was 3.55 and 7.06 with 4.95 and 6.87 as the standard deviation in the moderate and severe pain category respectively, the value of "p" being more than 0.001.

The fall of blood pressure and pulse rate is statistically significant. Though the fall was significant however it was of no clinical consequence.

A similar slight but statistically significant fall was noted by Lundstam, Wahlander [40] and other in their study " effect of delofenac sodium in treatment of renal colic". Such a fall may be attributed to relaxation of accentuation of blood pressure following the relief of pain.

R.Mirrales, J.Cami [6] and other in their study "diclofenac versus dipyrone in acute renal colic" have reported a significant decrease in mean blood pressure (Systolic and diastolic) and the cardiac rate after analgesic treatment with diclofenac sodium. The observed decrease in blood pressure and cardiac rate occured at the same time as the relief of pain. This suggest that the first evaluation might have been influenced by the stress of the painful situation.

Side effects :

Out of the total three hundred and twenty five patients, drowsiness was reported by thirteen patients (4.03%) vomiting by nine patients (2.76%), nausea by seven patients (2.16%) and 3 patients (93%) complained of dry mouth.

The drugs commonly used for relief of acute renal/ureteric colic belong to the following groups.

a. Narcotic analgesic e.g. pethidine, pentazocine etc.

b. Non narcotic analgesic/antispasmodic combinations e.g. Baralgan.

c. Prostaglandin inhibiter : e.g. indomethacin, diclofenac sodium.

e. Narcotic analgesics

1. Pethidine is a synthetic morphine substitute its common side effects are :

Vomiting, dry mouth, blurred vision, sedation, but over dose can cause CNS stimulation (Tremors, convulsions), respiratory depression and pethidine dependence occurs.Laurence Pharma text book.

2. Pentazocine (Fortwin) : is an opiate antagonist and its common side effects are - nausea, vomiting dizziness, sweating, Hypertension, palpitations, tachycardia, CNS disturbances (Euphoria, dyspheria) withdrawl syndrome in addicts, it can also induce physical dependence. (Laurence Pharma text book).

b. Non narcotic analgesic/antispasmodic combination

1. Baralgan is a combination of dipyrone which is an analgesic, a benzaphenone component which is a smooth muscle relaxant and a diphenyl derivative which has a parasympatholytic action.

The common side effects are :- dyspepsia, epigastric discomfort, nausea, vomiting, paptic ulcer, skin rashes, euphoria, blurring of vision allergic agranteocytosis, blood dyscrasias, hypotension etc. (Laurence Pharma text book).

c. Prostaglandin inhibitor

1. Indomethacin : This is a indole acetic acid derivative and its common side effects are :- Nausea, vomiting, dyspepsia, peptic ulcer, Headache, giddiness, mental confusion, blurring of vision and depression etc.

Diclofenac sodium is a sodium salt of O (2.6 - diclorophenylamino) - Phenylacetic acid, its side effects as reported by Willkens 1985 (63).

Gastrointestinal (10.2%) e.g. Nausea/vomiting and gastric upset etc.
CNS (.3%) e.g. dizziness, drowsiness and headache.
Allergic or local (.4%) e.g. rash etc.
others (1.6%) e.g. visual disturbence, oedema etc.
Lundstam, Wahlander (40) and others in their study reported that the side effects were less common with diclofenac sodium than with spasmofen. Drowsiness and nausea were near about equally prevalent, condevably the long duration of pain, often with disturbed sleep, could explain the drowsiness and nausea/vomiting is common in attacks of renal/ureteric colic. Thus these symptoms should not necessarily be considered side effects of treatment. It is likely, however, that larger doses of narcotic analgesic would significantly increase the side effects.

In our study we have observed that the intramuscular injection of prostaglandin synthetase inhibitor diclofenac sodium is fairly effective in relieving pain of acute renal/ureteric colic.

It is suggested that this treatment looks an attractive alternative that might replace narcotic drugs in the routine management of this common disorder, because of effectivity and minimal side effects. However more clinical studies are required to make a final judgement about the drug.

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CONCLUSIONS

CONCLUSION

The present " clinicopathological study of acute renal colic and evaluation of diclofenac sodium as an analgesic " was carried out over a period one year from April, 1990 to April, 1991. The study was conducted on (325) Three hundred and twenty five admitted patients of acute renal/ureteric colic in M.L.B. Medical College,Hospital, Jhansi during the above period. Injection diclofenac sodium (Dicloren) 75 mg intremuscularly was given and its effects over acute renal/ureteric colic pain was observed. Following conclusions have been drawn from this present study.

1. Approximately we had 26070 admissions in one year, in this hospitals and out of this 720 patients were of acute renal/ureteric colic (2.77%).
2. Symptomatic acute renal/ureteric colic are more common in males than females, rate ratio being 3:1.
3. Acute renal/ureteric colic is more common in between 15-35 years of age (81.08%), with peak incidence between 26-35 years (45.54%).
4. Acute renal/ureteric colic is more common in Hindu population (88%) as compared to patients of other religions.
5. Acute renal/ureteric colic is more common in highly manually active persons (53.25%) like formers,

6. Acute renal/ureteric colic is more common in middle socio-economic class of persons (60.28%).
7. Acute renal/ureteric colic is more common in predominantly vegetarian people (62.12%).
8. Acute renal/ureteric colic is more common in persons who do not consume alcohol (79.08%).
9. Pain, burning during micturition and haematuria are leading symptoms, 100%, 49.56% and 21.84% respectively.
10. Red blood cells pus cells and epithelial cells are common microscopical examination findings in urine 40.92%, 21.85% and 19.22% respectively. However 45.26% had no findings in urine micerscopic examination.
11. Radio-opaque shadow in plain KUB X-ray is present only in (40.00%) cases. In rest 60% cases do not show any radio-opaque shadow. It is an important finding.
12. Ureteric stones are more common (57.70%) in comparison to kidney stones.
13. Ureteric stones are more common in lower 1/3 of ureter (24.62%) followed by upper ureter (20.77%).
14. Renal/ureteric stones are more common on right side (72.31%) than on left side (27.70%).
15. About 89.13% patients out of 92 patients in whom IVP was possible showed one or the other abnormality due to presence of stone.

16. One hundreds and seventy three patients (53.24%) are suffering from severe pain followed by moderate pain (46.76%). None of the patient reported mild pain.

17. The potential effect of injection diclofenac sodium in words of complete relief were more marked in severe pain category (90.17%) in comparison to moderate pain category (40.79%) after 15 minutes of injection.

18. The number of patients experencing complete relief at the end of 30 ninutes rose to 86.22% and 93.55% in moderate and severe pain category respectively. There was no patient who did not report relief.

19. There is noticeable decrease in blood pressure (systolic & diastolic) and pulse rate in both category after 30 minutes of injection, but difference in systolic blood pressure in severe category is 17.37 mmHg in comparison to moderate type 11.95mmHg However the fall in B.P. and pulse rate were not of clinical significance.

So from above study we can safely say that -

1. It is not essential to see a radio-opaque shadow in all the cases of acute renal/ureteric colic.
2. It is not essential to see abnormality in the urine in all the cases, suffering from Acute renal/ureteric

3. Injection diclofenac sodium is a very effective alternative with minimal of side effects in the treatment of acute renal/ureteric colic pain.

However further studies are required to make a final judgement on the above statements.

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